Extending visit intervals for clinically stable patients on antiretroviral therapy: multicohort analysis of HIV programs in Southern Africa

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Abstract

Background: WHO recommends differentiated antiretroviral therapy (ART) delivery with longer visit intervals for clinically stable patients. We examined time trends in visit frequency and associations between criteria for clinical stability and visit frequency in ART programs in Southern Africa.

Methods: We included adults on ART from four programs with viral-load monitoring, two programs with CD4 monitoring, and four programs with clinical monitoring of ART. We classified patients as clinically stable based on virological (viral load <1000 copies/mL), immunological (CD4 >200 cells/µL), or clinical (no current tuberculosis) criteria. We used Poisson regression and survival models to examine associations between criteria for clinical stability and the rate of clinic visits.

Results: We included 180,837 patients. There were trends towards fewer visits in more recent years and with longer ART duration. In all ART programs, clinically stable patients were seen less frequently than patients receiving failing ART, but the strengths of the association varied. Adjusted incidence-rate ratios (IRRs) comparing visit rates for stable patients with patients on failing ART were 0.82 (95% CI 0.73-0.90) for patients classified based on the virological criterion, 0.81 (0.69-0.93) for patients classified based on the clinical criterion, and 0.90 (0.85-0.96) for patients classified based on the immunological criterion for stability.

Conclusion: Differences in visit rates between stable patients and patients failing ART were variable and modest overall. Larger differences were seen in programs using virological criteria for clinical stability than in programs using immunological criteria. Greater access to routine viral-load monitoring may increase scale-up of differentiated ART delivery.

Keywords: HIV, differentiated antiretroviral therapy delivery, differentiated service delivery, differentiated care, stable patients, Africa.

Introduction

Since 2015 the World Health Organization (WHO) has recommended treating all people living with HIV, and today more than 20 million people are on antiretroviral therapy (ART) with the goal to expand ART to reach about 30 million by 2020.[1–4] WHO's 2016 HIV treatment guidelines recommend a differentiated care approach to meet the needs of a rapidly growing and increasingly diverse cohort of people on ART.[2] Differentiated care is a public health approach to adapting service delivery to patient needs.[2,5,6] Differentiated care has been widely adopted by countries with support from major donors including PEPFAR, the Global Fund, and the Bill & Melinda Gates Foundation.[7–9]

Differentiated appointment spacing, i.e. extending visit intervals for clinically stable patients to 3-6 months, is one of the key recommendations for differentiated care.[2] National guidelines of several Southern African countries introduced extended visit intervals for patients stable on ART long before this recommendation was adopted by WHO in 2016. For example, the 2004 South African National Antiretroviral Treatment Guidelines recommended that stable patients should be seen every 3 months.[10] In Malawi, 2-monthly follow-up visits for stable patients were introduced in 2006.[11]

HIV programs need simple and reliable criteria for identifying clinically stable patients to implement differentiated care models safely and effectively. Early versions of national treatment guidelines did not define criteria for clinical stability.[10,11] WHO 2017 criteria for defining clinically stable patients include receiving ART for at least one year, no adverse drug reactions, no current illness, a good understanding of lifelong adherence, and evidence of treatment success. Programs with routine viral-load monitoring are advised to use virological criteria as a marker of treatment success (i.e. two consecutive viral-load measurements below 1000 copies/mL), and programs with CD4 monitoring should use immunological criteria (i.e. rising CD4 cell counts or a CD4 cell count >200 cells/µL).[5,12] Programs without access to viral load or CD4 monitoring rely on clinical criteria to determine treatment success.[13,14]

We examined time trends in visit frequency in ART programs in Southern Africa from 2004 to 2017 to describe the scale-up of extended visit intervals. We studied associations between visit frequency and clinical, immunological, and virological criteria for clinical stability to explore whether health care workers used available monitoring tools to identify patients who could be seen less frequently.

Methods

Antiretroviral therapy programs

The International epidemiology Databases to Evaluate AIDS (IeDEA) is a global collaboration of ART programs. We included 10 ART programs that participate in the Southern African region of IeDEA (IeDEA-SA).[15] Data were collected at ART initiation (baseline) and each follow-up visit using standardized instruments. ART programs regularly transfer datasets to data centers at the Universities of Cape Town, South Africa, and Bern, Switzerland for data curation and statistical analysis. ART programs vary in size: some programs like Tygerberg or Lighthouse operate at one or two large urban clinics while other programs like CIDRZ support over 300 urban and rural clinics in several districts. Four cohorts from South Africa performed routine viral-load monitoring with viral-load testing and CD4 cell counts measured annually. In two programs from Zambia and Zimbabwe, patient monitoring was based mainly on annual CD4 cell counts, and viral loads were not routinely monitored. In four programs from Lesotho, Malawi, Mozambique, and Zimbabwe, monitoring was mainly based on clinical criteria.[16]

Outcomes and definitions

Our primary outcome was the rate of clinic visits. A clinic visit was defined as attendance at a health facility for clinical assessment or pharmacy refill. Gaps between visits longer than one year were regarded as unscheduled treatment interruptions. Programs were classified as viral-load monitoring programs if the majority of their patients had a viral load measured during the first year on ART. Programs that measured the CD4 cell count for the majority of their patients during the first time on ART were classified as using CD4 monitoring. All other programs were deemed to be using clinical monitoring.

Clinical stability was defined according to WHO's 2017 criteria.[5,6] We classified patients as clinically stable if they received ART for at least one year and met a criterion for clinical stability. We used a different criterion for clinical stability for each monitoring strategy: in programs with viral-load monitoring, we classified patients with a viral load of <1000 copies/mL as clinically stable; in programs with CD4 monitoring, patients with a CD4 cell count of >200 cells/µL were deemed clinically stable; and in programs using clinical monitoring, patients without current tuberculosis were classified as stable. Our definition of clinical stability in programs using clinical monitoring relied solely on diagnosis of tuberculosis because we had no data on symptoms of other HIV-related diseases or side effects. Patients on ART for at least one year who did not meet the criterion for clinical stability were classified as receiving a failing ART regimen. Clinical stability was defined as a time-varying covariate carried forward until a next laboratory measurement or OI start or end date was recorded. We categorized visit dates into four periods: calendar years 2004-2007, 2008-2011, 2012-2015, and 2016-2017. We used WHO criteria to define clinical stage.[17] We defined CD4 count at ART initiation as the value closest to the date of ART initiation within three months prior to and one month after initiation. CD4 cell counts were grouped into <200 cells/µL, 200-349 cells/µL, 350-500 cells/µL, and >500 cells/µL. Age at ART initiation was grouped into 16-24 years, 25-34 years, 35-49 years, and 50 years or older. Viral load at ART initiation was defined as the value closest to the date of ART initiation within six months before and seven days after ART initiation. Time on ART was categorized in years: 1, 2, 3, 4, and 5-10.

Participants

HIV-1 infected patients aged ≥16 years who initiated ART between January 2004 and September 2017 and had at least one visit after the first year of ART were eligible for analysis. We excluded patients with insufficient data to define clinical stability by 12 months on ART (i.e. patients from programs with viral-load monitoring without a viral-load measurement between 4-12 months after ART initiation, and patients from programs with CD4 monitoring without CD4 cell count measurement between 3-12 months after ART initiation) (Figure 1).

Statistical analysis

We used summary statistics to described characteristics of patients at ART. We estimated incidence-rate ratios (IRRs) and 95% confidence intervals (CI) for predictors of visit frequency using univariable and multivariable Poisson regression models. In Poisson regression, each visit represents an event and the time between two consecutive visits is the exposure time. We used robust standard errors to adjust for clustering of visits at the patient level. Patients were followed from one year after initiation of ART for up to 10 years. We examined the following predictors: calendar year, time on ART, CD4 cell count, WHO clinical stage and age at ART initiation, and treatment program. Calendar year and time on ART were assessed at each visit and modelled as time-varying covariates. We added a continuous predictor for the proportion of patients receiving efavirenz-based ART at a program to assess whether the use of less toxic regimen explained the relationship between calendar year and visit frequency.

We modelled associations between criteria for clinical stability and visit frequency in two steps to account for the heterogeneity between ART programs. We first ran multivariable Poisson regression models and estimated adjusted IRRs and 95% CIs for the effect of clinical stability on visit frequency in each ART program. Models adjusted for time on ART, CD4 cell count, WHO clinical stage and age at ART initiation, and calendar year. We then pooled IRRs by criterion for clinical stability using random effects meta-analysis. We present adjusted IRRs for the difference in the rate of visits between stable patients and patients failing ART in each treatment program in a forest plot.

Finally, we used multivariable flexible parametric survival analysis to examine time-dependent effects of clinical stability on the visit rate (i.e. varying effects of clinical stability over time on ART) and to show absolute differences in the rate of visits between stable patients and patients receiving failing ART. In this survival analysis, each visit after ART initiation represents a failure event and multiple visits per patient are treated as multiple failures. Patients remain at risk of experiencing subsequent events after failure. Each visit date after ART initiation marks the end of the previous time interval and the beginning of the next interval (i.e. gap between visits). We used Royston-Parmar models with restricted cubic splines and interaction terms between restricted cubic splines and predictors for clinical stability to model time-dependent effects.[18–20] We used robust standard errors to adjust for clustering of multiple failure events within patients. We ran separate models for each criterion for clinical stability and predicted and plotted adjusted hazard rates and 95% CIs for specific levels of covariates. Models included predictors for clinical stability, calendar year, CD4 cell count at ART initiation, age, gender, and treatment program.

Missing WHO clinical stage and CD4 cell count at ART initiation were included as a separate category in all models. Unscheduled treatment interruptions (i.e. one year gaps) were excluded from analyses. In sensitivity analysis, we set the duration of these intervals to the median visit interval for the treatment program and time on ART. Statistical analysis was done in Stata (Version 15, Stata Corporation, College Station, TX, USA).

Ethical considerations

Local review boards and ethics committees for each treatment program that provided data approved the use of the data included in this study. The Cantonal Ethics Committee of the Canton of Bern, Switzerland, approved data merging and the collaborative analyses. Local review boards and the Cantonal Ethics Committee of the Canton of Bern waived the requirement to obtain informed consent.

Results

Characteristics of patients and ART programs

As shown in Table 1, we included 180,837 patients from 10 ART programs in seven countries: 38,045 (21.0%) patients came from four programs with viral-load monitoring; 85,555 (47.3%) from two programs with CD4 monitoring; and 57,237 (31.7%) from six programs with clinical monitoring. In South African ART programs, EFV-based ART was used for at least half of patients since 2005. The proportion of patients receiving EFV-based ART increased further with the phase out of stavudin (d4T) in 2010-2011. Most other programs widely introduced EFV-based ART as standard first-line regimen in 2013-2014 (Figure S1). We followed patients from January 1, 2004 up to August 31, 2017 for 876,801 person-years. Median follow-up time was 4.36 years (interquartile range [IQR] 2.55-6.88). Median age at ART initiation was 35 years (IQR 30-42), and 117,240 (64.8%) of included patients were female. Median CD4 cell count at ART initiation was 171 cells/µL (IQR 91-264). Almost half of the patients with known WHO clinical stage (46.3%, 68,901 of 148,809 patients) initiated ART in stage 3 or 4.

Predictors of visit frequency

Table 2 shows unadjusted and adjusted IRRs for predictors of visit frequency in programs using viral-load monitoring, CD4 monitoring, and clinical monitoring. There was a trend towards fewer visits in more recent years across all monitoring strategies. Rates of visits declined especially after 2011. Adjusted IRRs for the years 2012-2015 compared to years 2004-2007 were 0.75 (95% CI 0.75-0.76) in programs using viral-load monitoring, 0.54 (CI 0.54-0.55) in programs using CD4 monitoring, and 0.77 (CI 0.76-0.78) in programs using clinical monitoring. Time on ART and treatment program were also associated with visit frequency. Age, gender, and WHO clinical stage at ART initiation were weakly associated with visit rate. In viral load and CD4 monitoring programs a higher CD4 cell counts at the start of ART was associated with a slightly lower visit frequently. Adjusted IRRs for the change in visit frequency per 100% increase in the proportion of patients receiving EFV-based ART were 0.64 (CI 0.62-0.66) in programs using viral-load monitoring, 0.56 (CI 0.55-0.57) in programs using CD4 monitoring, and 0.88 (CI 0.88-0.89) in programs using clinical monitoring. The proportion of patients receiving EFV-based ART partially explained the relationship between calendar year and visit frequency. After controlling for the proportion of patients receiving EFV-based ART, adjusted IRRs for the years 2016-2017 compared to years 2004-2007 changed from 0.68 (CI 0.68-0.69) to 0.74 (CI 0.73-0.74) in programs using viral-load monitoring, from 0.61 (CI 0.60-0.61) to 0.88 (CI 0.87-0.89) in programs using CD4 monitoring, and from 0.69 (CI 0.69-0.70) to 0.77 (CI 0.76-0.78) in programs using clinical monitoring (Table S1)

Clinical stability and visit frequency

Clinically stable patients were seen less frequently than patients receiving failing regimens. Pooled adjusted IRRs comparing visit rates for clinically stable patients with patients on failing ART were 0.82 (95% CI 0.73-0.90) for patients classified based on the virological criterion, 0.81 (0.69-0.93) for patients classified based on the clinical criterion, and 0.90 (0.85-0.96) for patients classified based on the immunological criterion for clinical stability. Stable patients were seen less frequently than patients on failing regimens in all treatment programs, but as shown in Figure 2 the strength of the association varied considerably.

Figure 3 shows the adjusted hazard rate of visits by criteria for clinical stability. Stable patients were seen less frequently than individuals on a failing ART regimen in programs using virological, immunological and clinical monitoring. However, absolute differences varied: differences were much larger for patients classified based on virological and clinical criteria than for patients classified based on the immunological criterion (about 0.5 visits compared to 2 visits per year). The same pattern was seen when we predicted the visit rate for other calendar years, treatment programs, or baseline CD4 cell counts.

Our results were not sensitive to the strategies for handling unscheduled treatment interruptions (i.e. exclusion or replacement with medians).

Discussion

WHO has recently recommended longer visit intervals for clinically stable patients on ART,[2] and countries have widely adopted differentiated ART delivery[7–9] to ensure effectiveness and sustainability of HIV programs and to reduce the burden of care for patients and clinics.[21–25] The frequency of visits is an important measure of the effectiveness of ART delivery and associations between criteria for clinical stability and visit frequency indicate the level of differentiation of visit intervals.[26] In this study, we described trends in the frequency of visits between 2004 and 2017 in 10 HIV programs in Southern Africa and examined associations between virological, immunological and clinical criteria for clinical stability and the rate of clinic visits.

We observed a clear trend toward fewer visits in recent years that was independent of patients' clinical and immunological stage at the start of ART. This trend was partially explained by the proportion of patients receiving EFV-based ART. The virological and clinical criteria for clinical stability were moderately associated with the rate of visits, but the immunological criterion for clinical stability and other patient characteristics including WHO stage at ART initiation, gender, and age were only weakly associated. The association of fewer visits among stable patients was consistently found across all treatment programs, but the strength of the association varied considerably.

One possible explanation for time trends in visit frequency is that patients' better health at the start of ART in recent years allowed programs to extend visit intervals. WHO progressively increased the CD4 cell count thresholds for ART eligibility, and the median CD4 cell count of patients at the start of ART increased substantially over the last decade.[17,27–31] However, we adjusted our analysis for WHO clinical stage and CD4 cell count at ART initiation, and trends in visit frequency remained after controlling for these factors. Our data do not therefore support the hypothesis that trends in appointment spacing are driven by changes in ART eligibility criteria. We believe that other causes like the introduction of less toxic first-line regimens after 2010 and the widespread introduction of multi-month prescriptions were the drivers of the reduction in visit frequency.[14,17,32] The finding that the trend towards fewer visits in recent years was partially explained by the proportion of patients receiving EFV-based ART supports our hypothesis that the introduction of less toxic first-line regimen were one of the reasons for the reduction in visit frequency.

To implement differentiated ART delivery safely and effectively, programs need simple and reliable criteria for identifying clinically stable patients. Despite limited access to viral-load testing in several countries in this analysis, we see little evidence that programs were willing to use immunological criteria to differentiate visit intervals. In contrast, there was stronger evidence for differentiated appointment spacing based on virological and clinical criteria. A recent study from Zambia confirms our finding of little differentiation of appointment intervals based on immunological criteria. For every 50 cells/µL increase in CD4 count, time between appointments increased by only one day.[32] Sensitivity and positive predictive value of immunological criteria for identifying individuals with virological treatment failure are low[33] and caregivers may be reluctant to extend visit intervals based on these criteria as they may fear that virologically failing patients may not get the care they need.

The need for simple criteria for clinical stability and continued on-site supervision and mentoring to strengthen adherence to guidelines is further reinforced by data from Malawi that suggest that differentiating appointment spacing based on a complex set of criteria may not be feasible.[14] According to Malawi's national guidelines, patients are eligible for three-month ART refills if they meet the following criteria: 18 years or older, on first-line ART, no adverse drug reaction, no current illness or opportunistic infection, good adherence, and if viral-load testing was done then viral load <1000 copies/mL.[13] A recent evaluation of differentiated ART delivery in Malawi shows that these criteria were not widely applied. A large proportion of eligible individuals did not receive three-month ART refills, but many patients who were ineligible had been switched to extended refill intervals. In a large number of facilities, an equally large proportion of eligible and ineligible patients received three-month refills.[14]

Our data suggest that caregivers are comfortably extending visit intervals for virologically suppressed patients. Viral load is a direct measure of treatment adherence and treatment efficacy that is easy to interpret and well trusted by healthcare workers. The study from Zambia showed that clinical stability is a highly transient state. Regimen switching, severe immunodeficiency, and new WHO Stage III/IV disease were common among patients who had reached clinical stability.[32] Viral load enables early detection of treatment failure and early intervention.[34,35] Despite additional costs for viral-load tests, differentiated care based on viral monitoring is a cost-effective strategy in low-resource settings.[22] However, scale-up of viral-load testing is complex and routine viral-load testing is not yet widely available in many resource limited settings,[36,37]and even where viral-load testing has been implemented, the results may not improve clinical management if not delivered in a timely manner or acted upon when making clinical decisions.[34,38,39]

In the last decade, visit frequency has decreased substantially. Visits are anticipated to further decrease to six-month intervals as countries fully implement the WHO 2016 guidelines for differentiated care.[2] Widespread implementation of the most recent guidelines only began in mid-2016 and our study had insufficient follow-up time to explore the impact of the latest guideline change. Full implementation of the WHO 2016 guidelines has the potential to reduce the burden of treatment for patients, improve retention in care, decongest clinics, and reduce costs.[22,23,40] The clinical and public health impact of differentiated care is an important area for future evaluation.

Our study included data from a broad range of treatment programs with different monitoring strategies and we could examine associations between virological, immunological, and clinical criteria for clinical stability and visit schedules. With long-term follow-up we could examine patterns in visit spacing from the beginning of the scale-up of ART in Africa until 2017. Among the study's limitations, multi-month ART prescribing for stable patients on ART is a complementary approach to differentiated service delivery that is being increasingly adopted in sub-Saharan Africa.[14,23] We also had insufficient data to distinguish between visits with clinical consultation and pharmacy refill visits without clinical consultation, and therefore could not evaluate the potential benefit of fewer clinical follow-up visits. We had insufficient data on adverse drug reactions and adherence, and could not consider these criteria in our definition of clinical stability. Although our study included data from a large number of urban and rural primary, secondary and tertiary facilities, the programs participating in IeDEA may not be representative of the national ART program in the different countries. Finally, we had little data on opportunistic infections after start of ART, and our definition of clinical stability in clinical monitoring programs relied solely on diagnoses of current tuberculosis.

ART programs in Southern Africa reduced visit frequency over the last decade. Differences in visit rates between stable patients and patients failing ART were variable and modest overall. Because larger differences were seen particularly in programs using virological rather than immunological criteria for stability, we conclude that greater access to routine viral-load monitoring may increase scale-up of differentiated ART delivery.

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Table 1 Patient characteristics at initiation of antiretroviral therapy

	Monitoring Strategy						Total	
	Viral-load monitoring		CD4 monitoring		Clinical monitoring			
Number of patients (%)	38,045	(21.0%)	85,555	(47.3%)	57,237	(31.7%)	180,837	(100.0%)
Age (years)								
16-24	2,228	(5.9%)	6,968	(8.1%)	5,376	(9.4%)	14,572	(8.1%)
25-34	15,861	(41.7%)	33,659	(39.3%)	21,337	(37.3%)	70,857	(39.2%)
35-49	16,610	(43.7%)	37,201	(43.5%)	23,457	(41.0%)	77,268	(42.7%)
50+	3,346	(8.8%)	7,727	(9.0%)	7,067	(12.3%)	18,140	(10.0%)
Median (IQR)	35	(30-42)	35	(30-41)	35	(29-43)	35	(30-42)
Gender								
Male	12,731	(33.5%)	30,526	(35.7%)	20,340	(35.5%)	63,597	(35.2%)
Female	25,314	(66.5%)	55,029	(64.3%)	36,897	(64.5%)	117,240	(64.8%)
Year of ART initiation								
2004-2006	10,426	(27.4%)	11,275	(13.2%)	4,117	(7.2%)	25,818	(14.3%)
2007-2010	15,273	(40.1%)	37,999	(44.4%)	19,488	(34.0%)	72,760	(40.2%)
2011-2013	8,961	(23.6%)	22,883	(26.7%)	22,408	(39.1%)	54,252	(30.0%)
2014-2015	3,385	(8.9%)	13,136	(15.4%)	11,224	(19.6%)	27,745	(15.3%)
2016-2017	0	(0.0%)	262	(0.3%)	0	(0.0%)	262	(0.1%)
WHO stage								
1	15,459	(45.1%)	24,927	(32.1%)	8,735	(23.7%)	49,121	(33.0%)
2	3,625	(10.6%)	18,378	(23.7%)	8,784	(23.8%)	30,787	(20.7%)
3	10,907	(31.8%)	31,240	(40.2%)	16,368	(44.4%)	58,515	(39.3%)
4	4,288	(12.5%)	3,100	(4.0%)	2,998	(8.1%)	10,386	(7.0%)
Missing	3,766	(9.9%)	7,910	(9.2%)	20,352	(35.6%)	32,028	(17.7%)
CD4 cell count (cells/µL)								
<200	21,089	(72.5%)	38,095	(57.2%)	15,537	(52.7%)	74,721	(59.7%)
200-349	6,309	(21.7%)	20,178	(30.3%)	10,635	(36.1%)	37,122	(29.7%)
350-500	1,129	(3.9%)	5,164	(7.8%)	2,208	(7.5%)	8,501	(6.8%)
>500	567	(1.9%)	3,145	(4.7%)	1,094	(3.7%)	4,806	(3.8%)
Median (IQR)	136	(60-209)	179	(100-276)	190	(104-287)	171	(91-264)
Not measured	8,951	(23.5%)	18,973	(22.2%)	27,763	(48.5%)	55,687	(30.8%)
Viral load (log^{10} copies/ml)								
Median (IQR)	5	(4.4-5.5)	5	(4.4-5.5)	4.6	(3.3-5.3)	5	(4.4-5.5)
Not measured	30,699	(80.7%)	84,644	(98.9%)	56,686	(99.0%)	172,029	(95.1%)

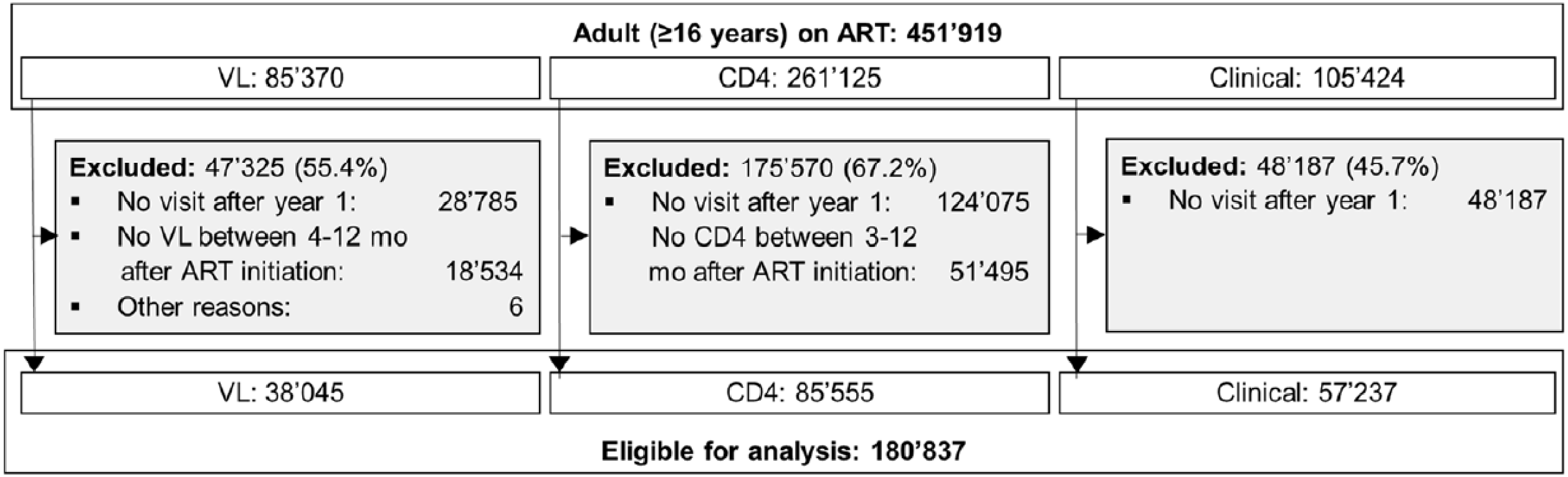
Data are number (percent) of patients if not stated otherwise. ART, antiretroviral therapy; IQR, interquartile range; WHO stage and CD4 cell count were assessed at initiation of ART.

Table 2 Predictors of visit frequency

	Univariable analyses			Multivariable analyses		
	VL	**CD4**	**Clinical**	**VL**	**CD4**	**Clinical**
	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)
Calendar year						
2004-2007	1	1	1	1	1	1
2008-2011	0.86 (0.85-0.86)	0.78 (0.77-0.79)	0.90 (0.89-0.91)	0.92 (0.91-0.92)	0.84 (0.83-0.84)	0.89 (0.88-0.90)
2012-2015	0.68 (0.67-0.68)	0.46 (0.46-0.47)	0.77 (0.76-0.78)	0.75 (0.75-0.76)	0.54 (0.54-0.55)	0.77 (0.76-0.78)
2016-2018	0.63 (0.62-0.64)	0.50 (0.50-0.51)	0.67 (0.66-0.68)	0.68 (0.68-0.69)	0.61 (0.60-0.61)	0.69 (0.69-0.70)
Year on ART						
2	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
3	0.93 (0.93-0.94)	0.92 (0.92-0.93)	0.93 (0.93-0.93)	0.96 (0.96-0.96)	0.97 (0.96-0.97)	0.94 (0.94-0.95)
4	0.89 (0.89-0.89)	0.84 (0.83-0.84)	0.90 (0.90-0.91)	0.95 (0.94-0.95)	0.91 (0.91-0.92)	0.93 (0.93-0.94)
5+	0.81 (0.81-0.81)	0.68 (0.68-0.69)	0.84 (0.84-0.85)	0.92 (0.91-0.92)	0.84 (0.84-0.84)	0.90 (0.89-0.90)
Age at ART initiation						
15-24	1	1	1	1	1	1
25-34	0.98 (0.96-0.99)	0.99 (0.97-1.00)	0.96 (0.95-0.97)	0.98 (0.96-0.99)	0.99 (0.98-1.00)	0.97 (0.96-0.98)
35-49	0.96 (0.94-0.97)	1.01 (1.00-1.03)	0.97 (0.96-0.98)	0.98 (0.96-0.99)	1.01 (1.00-1.02)	0.98 (0.97-0.99)
50+	0.96 (0.94-0.98)	1.04 (1.03-1.06)	1.04 (1.02-1.05)	1.00 (0.99-1.02)	1.04 (1.03-1.05)	1.01 (1.00-1.02)
Gender						
Male	1	1	1	1	1	1
Female	1.01 (1.00-1.01)	0.98 (0.97-0.98)	1.04 (1.03-1.04)	1.01 (1.01-1.02)	0.99 (0.99-1.00)	1.03 (1.03-1.04)
WHO clinical stage						
1	1	1	1	1	1	1
2	1.03 (1.02-1.04)	1.12 (1.11-1.13)	1.01 (1.00-1.02)	1.00 (0.99-1.01)	1.04 (1.03-1.04)	1.01 (1.00-1.02)
3	1.08 (1.07-1.09)	1.15 (1.14-1.16)	0.96 (0.95-0.97)	1.03 (1.02-1.04)	1.04 (1.03-1.05)	1.01 (1.01-1.02)
4	1.10 (1.08-1.11)	1.25 (1.23-1.27)	1.02 (1.00-1.03)	1.03 (1.02-1.04)	1.06 (1.05-1.07)	1.06 (1.04-1.07)
Unknown	1.62 (1.60-1.65)	1.10 (1.09-1.12)	0.85 (0.84-0.86)	1.03 (0.99-1.07)	1.06 (1.05-1.06)	1.00 (0.99-1.00)
CD4 at ART initiation						
<200	1	1	1	1	1	1
200-349	0.90 (0.90-0.91)	0.89 (0.88-0.89)	1.04 (1.03-1.05)	0.96 (0.95-0.97)	0.94 (0.94-0.95)	1.01 (1.00-1.01)
350-500	0.89 (0.87-0.91)	0.84 (0.83-0.85)	1.06 (1.04-1.08)	0.96 (0.94-0.98)	0.92 (0.91-0.93)	1.00 (0.99-1.02)
>500	0.88 (0.86-0.91)	0.81 (0.80-0.82)	1.10 (1.08-1.13)	0.94 (0.92-0.95)	0.89 (0.87-0.90)	1.00 (0.98-1.02)
Unknown	1.02 (1.01-1.03)	0.90 (0.89-0.90)	0.95 (0.95-0.96)	0.99 (0.99-1.00)	0.96 (0.95-0.96)	1.01 (1.00-1.01)

Data are incidence rate ratios (IRR) and 95% confidence intervals (CIs) from univariable and multivariable Poisson models. Clinical, Clinical monitoring; CD4, CD4 monitoring; VL, Viral-load monitoring. Calendar year and years since antiretroviral therapy (ART) initiation were assessed at each visit. CD4 cell count, WHO clinical stage, and age were measured at initiation of antiretroviral therapy (ART). Multivariable model is adjusted for all variables shown in the table and treatment program.

Figure 1 Flow of eligibility of patients



Data are number (%) of patients.
Clinical, Clinical monitoring; CD4, CD4 monitoring; VL, Viral-load monitoring
ART, Antiretroviral therapy; Mo, Months.

Figure 2 Forest plot of incidence-rate ratios comparing clinically stable patients and patients receiving failing regimens

Forest plot of adjusted incidence-rate ratios (IRRs) comparing visit rates between clinically stable patients and patients receiving failing antiretroviral therapy (ART) regimens in 10 treatment programs in Southern Africa. Patients from programs using viral-load monitoring were classified based on a virological criterion for clinical stability, patients from programs using CD4 monitoring were classified based on an immunological criterion for clinical stability, and patients from programs using clinical monitoring were classified based on a clinical criterion for clinical stability. IRRs are adjusted for calendar year, time on ART, CD4 cell count, age, WHO clinical stage at ART initiation, and gender. Separate models were fitted for each treatment program and estimates were pooled by criterion for clinical stability using random effects meta-analysis. N, Number of patients in each treatment program at the beginning of follow-up (i.e. one year after initiation of ART).

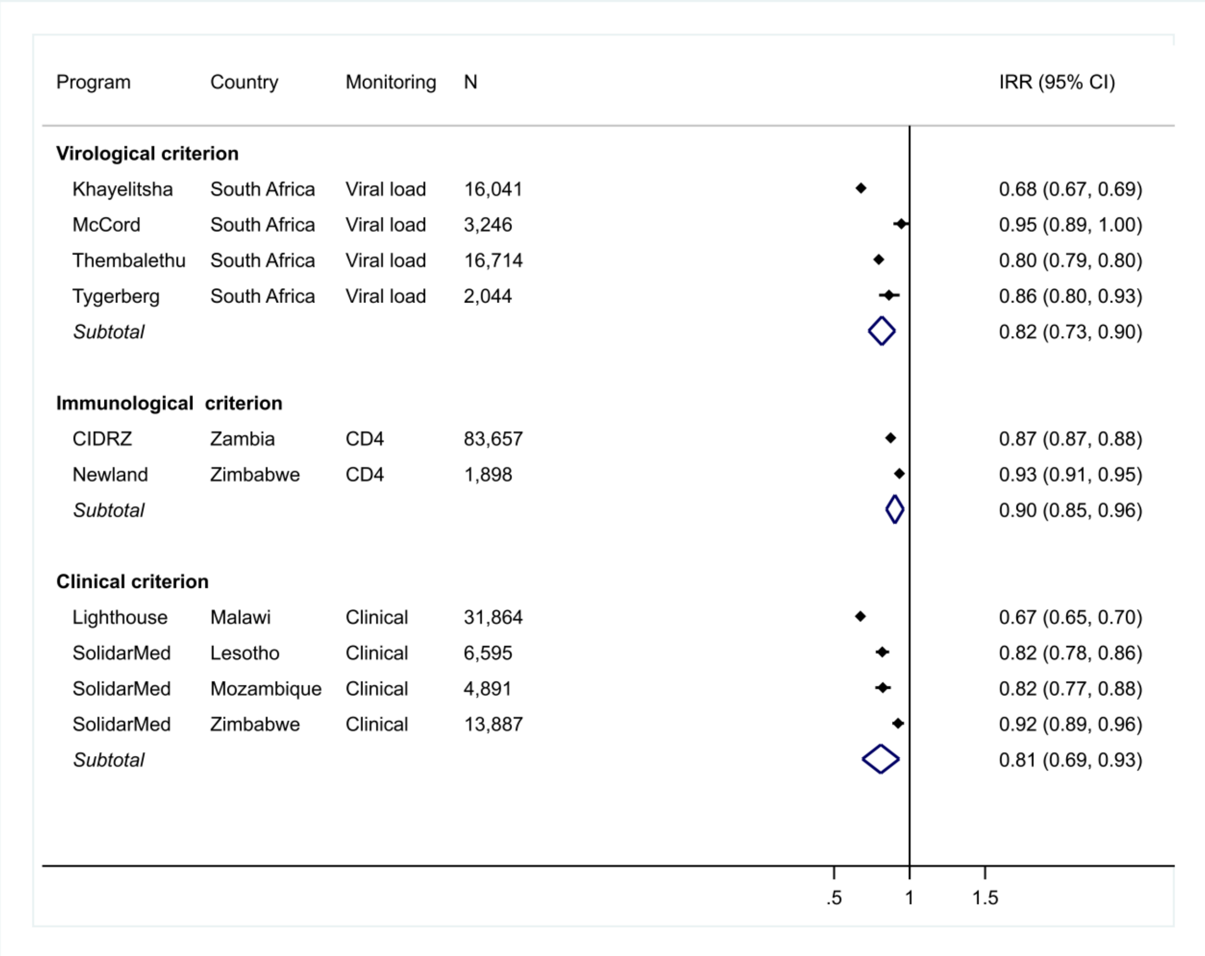
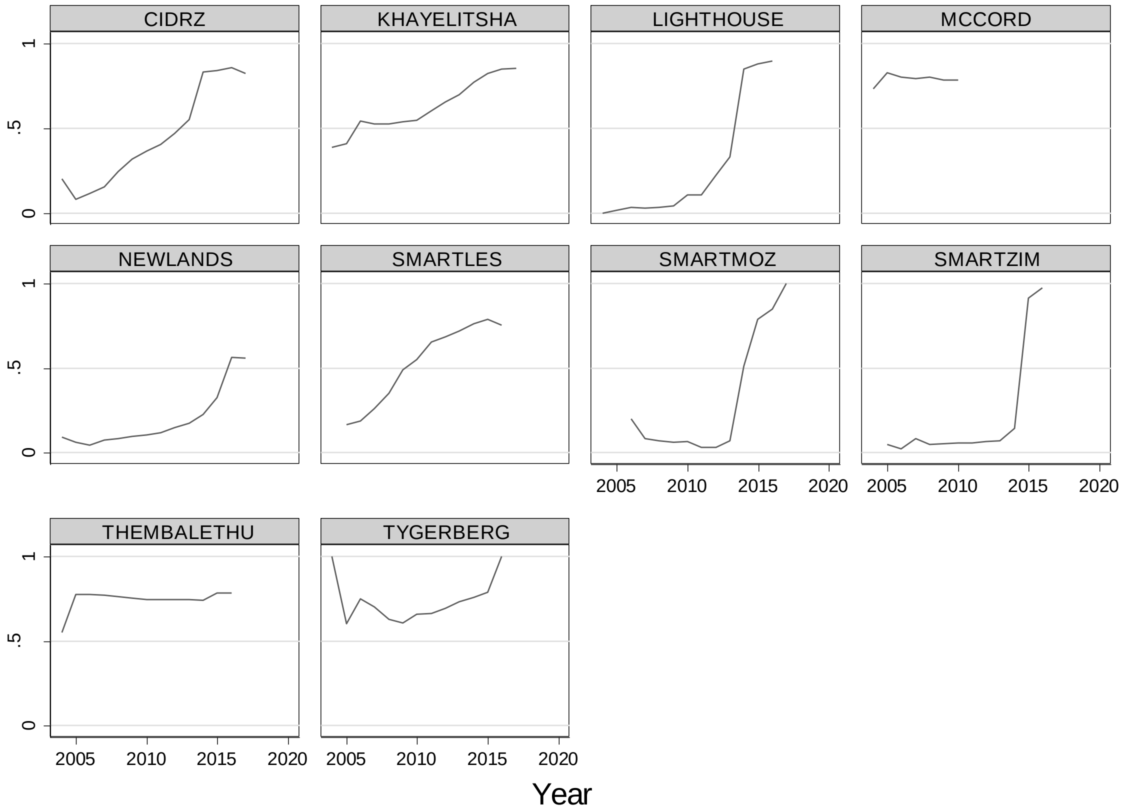


Figure 3 Rate of visits by clinical stability

Adjusted hazard rates of visits per year (solid lines) and 95% confidence intervals (dashed lines) for clinically stable patients and patients receiving failing ART regimens. Patients from programs using viral-load monitoring were classified based on a virological criterion for clinical stability, patients from programs using CD4 monitoring were classified based on a immunological criterion for clinical stability, and patients from programs using clinical monitoring were classified based on a clinical criterion for clinical stability. Models adjusted for clinical stability, calendar year, CD4 cell count at ART initiation, age, gender, and treatment program. Hazard rates were predicted for years 2016-2017 for 25-34 years old female patients starting ART with a CD4 cell count of 200-349 cells/µL at the largest treatment program using the respective monitoring strategy.



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Author contributions

AH wrote the first draft of the study protocol, which was revised by LJ and ME; all authors critically reviewed the study protocol and contributed to its final version. AH did statistical analyses, with interpretation of results by all authors. LJ advised on statistical analysis. AH wrote the first draft of the report, which was revised by LJ, AG, NF, ME, CM, JE, HP, MPF, MvL, and MH. MPF, JE, MvL, HP, IS, CC & CK assisted in implementation, fieldwork, and data collection at study sites. ME obtained funding for the project. All authors reviewed and approved the final version for submission.

Supplementary appendix

Table S1: Predictors of visit frequency controlling for proportion of patients receiving efavirenz-based antiretroviral therapy.

	VL IRR (95% CI)	CD4 IRR (95% CI)	Clinical IRR (95% CI)
Univariable analyses			
Proportion of patients receiving EFV			
per 100% increase	0.39 (0.38-0.41)	0.31 (0.30-0.31)	0.86 (0.85-0.86)
Multivariable analyses			
Calendar year			
2004-2007	1	1	1
2008-2011	0.92 (0.91-0.93)	0.93 (0.92-0.94)	0.90 (0.89-0.91)
2012-2015	0.78 (0.78-0.79)	0.71 (0.71-0.72)	0.81 (0.80-0.82)
2016-2018	0.74 (0.74-0.75)	0.88 (0.87-0.89)	0.77 (0.76-0.78)
Year on ART			
2	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
3	0.96 (0.96-0.96)	0.97 (0.96-0.97)	0.94 (0.94-0.95)
4	0.95 (0.94-0.95)	0.92 (0.91-0.92)	0.93 (0.93-0.94)
5+	0.92 (0.91-0.92)	0.86 (0.86-0.87)	0.91 (0.90-0.91)
Age at ART initiation			
15-24	1	1	1
25-34	0.98 (0.97-0.99)	0.99 (0.98-1.00)	0.97 (0.96-0.98)
35-49	0.98 (0.97-0.99)	1.01 (1.00-1.02)	0.97 (0.96-0.98)
50+	1.00 (0.99-1.02)	1.04 (1.03-1.05)	1.01 (1.00-1.02)
Gender			
Male	1	1	1
Female	1.01 (1.01-1.02)	0.99 (0.99-1.00)	1.03 (1.03-1.04)
WHO clinical stage			
1	1	1	1
2	1.00 (0.99-1.02)	1.03 (1.02-1.03)	1.01 (1.00-1.02)
3	1.03 (1.02-1.03)	1.02 (1.02-1.03)	1.00 (1.00-1.01)
4	1.02 (1.01-1.03)	1.04 (1.03-1.05)	1.05 (1.03-1.06)
Unknown	1.04 (1.00-1.08)	1.06 (1.06-1.07)	0.99 (0.99-1.00)
CD4 at ART initiation			
<200	1	1	1
200-349	0.96 (0.96-0.97)	0.95 (0.94-0.95)	1.01 (1.00-1.02)
350-500	0.96 (0.94-0.98)	0.93 (0.92-0.94)	1.01 (0.99-1.02)
>500	0.94 (0.92-0.96)	0.90 (0.89-0.91)	1.00 (0.98-1.02)
Unknown	0.99 (0.98-1.00)	0.97 (0.96-0.98)	1.01 (1.01-1.02)
Proportion of patients receiving EFV			
per 100% increase	0.64 (0.62-0.66)	0.56 (0.55-0.57)	0.88 (0.88-0.89)

Data are incidence rate ratios (IRR) and 95% confidence intervals (CIs) from univariable and multivariable Poisson models. Clinical, Clinical monitoring; CD4, CD4 monitoring; VL, Viral-load monitoring. Calendar year and years since antiretroviral therapy (ART) initiation were assessed at each visit. CD4 cell count, WHO clinical stage, and age were measured at initiation of antiretroviral therapy (ART). Proportion of patients receiving efavirenz (EFV)-based antiretroviral therapy regimen at a treatment program in calendar year. Multivariable model is adjusted for all variables shown in the table and treatment program.

Figure S1: Proportion of patients receiving efavirenz-based antiretroviral therapy.